

SUPPLEMENTARY MATERIAL

Long term safety and efficacy of macitentan in inoperable chronic
thromboembolic pulmonary hypertension: Results from MERIT and its open-label extension

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Supplementary Methods 1

List of Study sites, Review boards and Committees

a). MERIT-2 investigators

This list includes all sites participating in the MERIT-2 open-label period

Country	Site ID	Organisation	Principal Investigator
Belgium	1102	UNIVERSITY HOSPITAL GASTHUISBERG - PNEUMOLOGIE (Leuven)	Delcroix, Marion
Germany	1401	UNIVERSITÄTSKLINIKUM GIESSEN - PNEUMOLOGIE (Giessen)	Ghofrani, Ardeschir
Germany	1402	MISSIONSÄRZTLICHE KLINIK WÜRZBURG (Würzburg)	Held, Matthias
Germany	1404	UNIVERSITÄTSKLINIKEN DES SAARLANDES - INNERE MEDIZIN (Homburg/Saar)	Wilkens, Heinrike
Germany	1406	UNIVERSITÄTSKLINIKUM HEIDELBERG THORAXKLINIK (Heidelberg)	Grünig, Ekkehard
United Kingdom	2101	HAMMERSMITH HOSPITAL, DEPARTMENT OF CARDIOLOGY (London)	Howard, Luke
United Kingdom	2102	ROYAL PAPWORTH HOSPITAL NHS FOUNDATION TRUST (Cambridge)	Pepke-Zaba, Joanna
United Kingdom	2104	ROYAL HALLAMSHIRE - PULM VASCULAR MED (Sheffield)	Condliffe, Robin
France	2201	HOSP BICETRE - DEPT PULMO & RESP INTENSIVE CARE (Le Kremlin-Bicêtre cedex)	Jais, Xavier
France	2202	HOSP LARREY - DPT PNEUMOLOGY (Toulouse Cedex 9)	Prévot, Grégoire
France	2207	HOSP MICHALLON - DEPT CARDIOLOGY (Grenoble cedex 9)	Bouvaist, Hélène
France	2208	HOSP POMPIDOU - DEPT PNEUMOLOGY AND INTENSIVE CARE (Paris cedex 15)	Sanchez, Olivier
Switzerland	2401	UNIV HOSP ZURICH DEPT PNEUMO (Zürich)	Speich, Rudolf
Czech Republic	3301	CHARLES UNI PPH CENTRE (Praha 2)	Jansa, Pavel
Hungary	3401	SEMMELEWIS UNIV - PULMONOLOGY (Budapest)	Karlócai, Kristóf
Hungary	3405	UNIV DEBRECEN CARD CLIN (Debrecen)	Edes, Istvan
Lithuania	350	VILNIUS UNI PULMONARY HYPERTENSION CENTER (Vilnius)	Aidietiene, Sigita
Lithuania	3502	KAUNAS HOSPITAL OF LITHUANIAN UNIV OF HEALTH PULMONOLOGY (Kaunas)	Miliauskas, Skaidrius

Poland	3601	CARDIOLOGY WROCLAW (Wrocław)	Lewczuk, Jerzy
Poland	3605	CARDIOLOGY POZNAŃ UNIV (Poznań)	Mularek-Kubzdela, Tatiana
Poland	3607	CARDIOLOGY LUBLIN STATE (Lublin)	Grzywna, Ryszard
Russian Federation	3800	FEDERAL NORTH-WEST MEDICAL RESEARCH CENTER N.A. V.A.ALMAZOV (St. Petersburg)	Moiseeva, Olga M
Russian Federation	3801	NOVOSIBIRSK SCIENTIFIC RESEARCH INST N.A. E.N. MESHALKIN (Novosibirsk)	Chernyavskiy, Alexander
Russian Federation	3802	CARDIOLOGY SCIENTIFIC RESEARCH INSTITUTE (Tomsk)	Shipulin, Vladimir
Russian Federation	3806	SCI INSTITUTE SYSTEMIC PROBLEMS CARDIO DISEASES KEMEROVO (Kemerovo)	Barbarash, Olga
Russian Federation	3807	RUSSIAN CARDIOLOGY SCIENTIFIC AND PRODUCTION COMPLEX (Moscow)	Martynyuk, Tamila
Ukraine	4100	LVIV REG CLIN HOSP, CARDIOSURGERY (Lviv)	Solovey, Lyubomyr
Ukraine	4101	STATE INST OF PHTHYSIOLOGY AND PULM, YANOVSKIY OF AMS (Kyiv)	Gavrysyuk, Volodymyr
Turkey	4202	ISTANBUL UNIV HOSP MED (Capa Istanbul)	Okumus, Gulfer
Vietnam	4801	HANOI MEDICAL UNIVERSITY HOSPITAL (Hanoi)	Nguyen, Lan Hieu
China	5101	CARDIOVASCULAR INSTITUTE&FUWAI HOSP-THROMBUS CENTER (Beijing)	Jing, Zhi-Cheng
China	5103	BEIJNG CHAO-YANG HOSP-DEPARTMENT OF RESPIRATION (Beijing)	Yang, Yuanhua
China	5104	SHANGHAI PULMONARY HOSPITAL, DEPT OF PULMONARY CIRCULATION (Shanghai)	Liu, Jinming
China	5107	WU HAN ASIA HEART HOSP (Wuhan)	Zhang, Gangcheng
China	5108	THE 1ST AFFILIATED HOSP OF GUANGZHOU MED UNIV-RESP DEPT (Guangzhou)	Zhang, Nuofu
China	5109	BEIJING ANZHEN HOSP,CAPTIAL MED UNIV-ICU (Beijing)	Mi, Yuhong
China	5110	THE GENERAL HOSP OF SHENYANG MILITARY REGION (Shenyang)	Zhu, Xianyang
Korea (South), Rep. Of	5301	SEVERANCE HOSPITAL, YONSEI UNIVERSITY HEALTH SYSTEM (Seoul)	Chang, Hyuk-Jae

Korea (South), Rep.Of	5302	SEOUL NATIONAL UNIVERSITY HOSPITAL (Seoul)	Kim, Hyung-Kwan
Korea (South), Rep.Of	5303	ASAN MED CTR (Seoul)	Lee, Jae Seung
Thailand	5701	MAHARAJ NAKORN CHIANG MAI HOSP, DEPT OF INT MED (Chiang Mai)	Phrommintikul, Arintaya
Thailand	5704	KING CHULALONGKORN MEMORIAL HOSP,DIV OF RESP & CRIT CARE MED (Bangkok)	Jaimchariyatam, Nattapong
Thailand	5705	SIRIRAJ HOSP MAHIDOL UNI, DIV OF RESP DISEASE & TUBERCULOSIS (Bangkok)	Sompradeekul, Suree
South Africa	6004	LUNG INFECTION & IMMUNITY UNIT (Cape Town)	Dheda, Keertan
Chile	8201	CLINICA TABANCURA - CARDIO UNIT (Santiago de Chile)	Sepulveda Varela, Pablo
Mexico	8401	INSTITUTO NACIONAL DE CARDIOLOGIA (INC) IGNACIO CHAVEZ (Mexico City)	Pulido Zamudio, Tomas Rene
Mexico	8402	UNIDAD DE INVESTIGACION CLIN EN MED, SC (UDICEM) (Monterrey)	Sanchez, Carlos Jerjes
USA	9122	UCSD MED CTR - PULM VASCULAR DIV (La Jolla)	Kerr, Kim

b). MERIT-2 institutional review boards and ethical committees

Country	IRB/EC Name/Address	Site	Approval Date
Belgium	Commissie Medische Ethiek UZ Gasthuisberg Commissie Medische Ethiek UZ Gasthuisberg, Uz Gasthuisberg - E330, HERESTRAAT 49, Leuven, 3000 Belgium	1102 Herestraat 49, 7th floor beige, Pneumology department, Campus Gasthuisberg Leuven, 3000 BELGIUM Received drug	Site, Region: / Site, Central: 22-Dec-14 Site, Local: /
China	Ethics Committee of Cardiovascular institute & Fuwai Hospital for Clinical Trials Ethics Committee of Cardiovascular institute & Fuwai Hospital for Clinical Trials, No#.167 North Lishi Road, Xicheng District, Beijing, 100037 China	5101 No. 167 North Lishi Road, Floor 11, New Building, Beijing, Xicheng District, 100037 CHINA Received drug	Site, Region: / Site, Central: / Site, Local: 15-Apr-15
China	Ethics Committee of Beijing Chaoyang Hospital Ethics Committee of Beijing Chaoyang Hospital, No.8 Gongti South Street, Chaoyang District, Beijing, 100043 China	5103 No.8, Gong Ti South Road,Chaoyang District, Beijing, 100020 CHINA Received drug	Site, Region: / Site, Central: / Site, Local: 16-Jun-15

China	IEC of Shanghai Pulmonary Hospital IEC of Shanghai Pulmonary Hospital, No. 507, Zhengmin Road, Yangpu District, Shanghai, Shanghai, 200433 China	5104 No. 507 Zhengmin Road, Yangpu District, Shanghai, 200433 CHINA Received drug	Site, Region: / Site, Central: / Site, Local: 21-Aug-15
China	EC of Wuhan Asia Heart Hospital EC of Wuhan Asia Heart Hospital, No. 753 Jingnan Avenue, Wuhan City, Hubei Province, Wuhan, Hubei, 430030 China	5107 No. 753 Jingnan Avenue, Wuhan City, Hubei Province, Wuhan, Hubei, 430022 CHINA Received drug	Site, Region: / Site, Central: / Site, Local: 31-Mar-16
China	EC of the 1ST AFFILIATED HOSPITAL OF GUANGZHOU MEDICAL UNIVERSITY EC of the 1ST AFFILIATED HOSPITAL OF GUANGZHOU MEDICAL UNIVERSITY, No.151, Yan Jiang Road, Guangzhou City, Guangzhou, 510120 China	5108 No.151, Yan Jiang Xi Road, Guangzhou City, Guangzhou, 510120 CHINA Received drug	Site, Region: / Site, Central: / Site, Local: 8-Oct-15
China	EC of The General Hospital of Shenyang Military Region EC of The General Hospital of Shenyang Military Region, Wenhua Road No.83, Shenhe District, Shenyang City, Liaoning Province, Shenyang, Liaoning, 110016 China	5110 No.83 Wenhua Road, Shenhe District, Shenyang City, Liaoning Province, Shenyang, Liaoning, 110016 CHINA Received drug	Site, Region: / Site, Central: / Site, Local: 30-Mar-16
Czechia	Etická komise Všeobecné fakultní nemocnice v Praze Etická komise Všeobecné fakultní nemocnice v Praze, Na Bojišti 1, Praha 2, 12808 Czechia	3301 li. Internal Clinic, U Nemocnice 2, Praha 2, 128 08 CZECHIA Received drug	Site, Region: 24-Apr-14 Site, Central: / Site, Local: 24-Apr-14
France	CPP Ile-de-France VII CPP Ile-de-France VII, Hôpital de Bicêtre, Portail des Champs, Porte 74 bis, RDC 78 rue du Général Leclerc, le Kremlin Bicêtre, 94270 France	2201 78 rue du General Leclerc, Centre De Reference De L'Hypertension Pulmonaire Severe, Service De Pneumologie Et Reanimation Respiratoire, Le Kremlin-Bicetre Cedex, 94275 FRANCE Received drug	Site, Region: / Site, Central: 25-Mar-14 Site, Local: /
France	CPP Ile-de-France VII CPP Ile-de-France VII, Hôpital de Bicêtre, Portail des Champs, Porte 74 bis, RDC 78 rue du Général Leclerc, le Kremlin Bicêtre, 94270 France	2202 24 Chemin de Pourville TSA 30031, Service De Pneumologie, Toulouse Cedex 9, 31059, FRANCE Received drug	Site, Region: / Site, Central: 25-Mar-14 Site, Local: /
France	CPP Ile-de-France VII CPP Ile-de-France VII, Hôpital de Bicêtre, Portail des Champs, Porte 74 bis, RDC 78 rue du Général Leclerc, le Kremlin Bicêtre, 94270 France	2208 20 rue Leblanc, Paris Cedex 15, 75908 FRANCE Received drug	Site, Region: / Site, Central: 25-Mar-14 Site, Local: /

Germany	Ethikkommission des Fachbereichs Medizin der Justus-Liebig-Universität Giessen Ethikkommission des Fachbereichs Medizin der Justus-Liebig-Universität Giessen, Klinikstrasse 29, Gießen, Hesse, 35385 Germany	1401 Klinikstrasse 33, Medizinische Klinik und Poliklinik II, PNEUMOLOGIE, , Giessen, 35392 GERMANY Received drug	Site, Region: / Site, Central: 14-Aug-14 Site, Local: /
Germany	Ethikkommission bei der Bayerischen Landesärztekammer Ethikkommission bei der Bayerischen Landesärztekammer, Mühlbaaurstr. 16, München, Bavaria, 81677 Germany	1402 Salvatorstrasse 7, Würzburg, 97074 GERMANY Received drug	Site, Region: / Site, Central: / Site, Local: 14-Aug-14
Germany	Ethik-Kommission I der Medizinischen Fakultät Heidelberg Ethik-Kommission I der Medizinischen Fakultät Heidelberg, Alte Glockengiesserei 11/1, Heidelberg, 69115 Germany	1406 Röntgenstrasse 1, Heidelberg, 69126 GERMANY Received drug	Site, Region: / Site, Central: / Site, Local: 14-Aug-14
Hungary	Medical Research Council Ethics Committee for Clinical Pharmacology Medical Research Council Ethics Committee for Clinical Pharmacology, Széchenyi István tér 7-8, Budapest, 1051 Hungary	3401 Tömő utca 25-29, Budapest, 1083 HUNGARY Received drug	Site, Region: 26-May-14 Site, Central: / Site, Local: /
Hungary	Medical Research Council Ethics Committee for Clinical Pharmacology Medical Research Council Ethics Committee for Clinical Pharmacology, Széchenyi István tér 7-8, Budapest, 1051 Hungary	3405 Moricz Zsigmond korut 22, Debrecen, 4032 HUNGARY Received drug	Site, Region: 26-May-14 Site, Central: / Site, Local: /
Lithuania	Lithuanian Bioethics Committee Lithuanian Bioethics Committee, Algirdo g. 31, Vilnius, LT-03219 Lithuania	3502 Eiveniu 2, Kaunas, 50161 LITHUANIA Received drug	Site, Region: 27-Jul-15 Site, Central: / Site, Local: /
Mexico	Comité de Ética en Investigación del Instituto Nacional de Cardiología "Ignacio Chávez" Comité de Ética en Investigación del Instituto Nacional de Cardiología "Ignacio Chávez", Juan Badiano #1, Colonia Sección XVI, Delegación Tlalpan, Mexico City, Mexico City, 14080 Mexico	8401 Juan Badiano No. 1, Colonia Seccion XVI, Delegacion Tlalpan, Ciudad de Mexico, Distrito Federal, 14000 MEXICO Received drug	Site, Region: / Site, Central: / Site, Local: 18-Feb-14
Poland	Komisja Bioetyczna przy Dolnoslaskiej Izbie Lekarskiej we Wroclawiu Komisja Bioetyczna przy Dolnoslaskiej Izbie Lekarskiej we Wroclawiu, Kazimierza Wielkiego	3601 ul. Kamieńskiego 73a, Wrocław, 51-124 POLAND Received drug	Site, Region: / Site, Central: 10-Jun-15 Site, Local: /

	45, Wrocław, 50-077 Poland		
Poland	Komisja Bioetyczna przy Dolnoslaskiej Izbie Lekarskiej we Wrocławiu Komisja Bioetyczna przy Dolnoslaskiej Izbie Lekarskiej we Wrocławiu, Kazimierza Wielkiego 45, Wrocław, 50-077 Poland	3607 al. Kraśnicka 100, Lublin, 20-718 POLAND Received drug	Site, Region: / Site, Central: 10-Jun-15 Site, Local: /
Russian Federation	Ethics Committee at the Federal State Budgetary Institution "Almazov National Medical Research Center" of the Ministry of Health of the Russian Federation Ethics Committee at the Federal State Budgetary Institution "Almazov National Medical Research Center" of the Ministry of Health of the Russian Federation, 2, Akkuratova ul., St. Petersburg, 197341 Russian Federation	3800 Akkuratova str., 2, St Petersburg, 197341 RUSSIAN FEDERATION Received drug	Site, Region: / Site, Central: / Site, Local: 20-Jan-15
Russian Federation	E.N. Meshalkin National Medical Research Center Ethics committee E.N. Meshalkin National Medical Research Center Ethics committee, 15, Rechkunovskaya str., Novosibirsk, 630055 Russian Federation	3801 15, Rechkunovskaya str, Novosibirsk, 630055 RUSSIAN FEDERATION Received drug	Site, Region: / Site, Central: / Site, Local: 10-Mar-15
Russian Federation	Biomedical Ethics Committee at Scientific-Research Institute of Cardiology of Federal state budget scientific institution 'Tomsk national research medical center of the Russian academy of sciences' Biomedical Ethics Committee at Scientific-Research Institute of Cardiology of Federal state budget scientific institution 'Tomsk national research medical center of the Russian academy of sciences', 111a, Kievskaya str., Tomsk, 634012 Russian Federation	3802 111a, Kievskaya str., Tomsk, 634012 RUSSIAN FEDERATION Received drug	Site, Region: / Site, Central: / Site, Local: 23-Jan-15
Russian Federation	Local Ethics Committee of Federal State Budgetary Institution "Scientific Research Institute of Systemic Problems of Cardiovascular Diseases" Local Ethics Committee of Federal State Budgetary Institution "Scientific Research Institute of Systemic Problems of Cardiovascular Diseases", 6, Sosnovy blv., Kemerovo, 650002 Russian Federation	3806 6 Sosnovy Boulevard, Kemerovo, 650002 RUSSIAN FEDERATION Received drug	Site, Region: / Site, Central: / Site, Local: 12-Mar-15

Russian Federation	Committee on Ethics Issues in Clinical Cardiology at the National Medical Research Center of Cardiology of the Ministry of Health of the Russian Federation Committee on Ethics Issues in Clinical Cardiology at the National Medical Research Center of Cardiology of the Ministry of Health of the Russian Federation, 15 A, 3-rd Cherepkovskaya Str., Moscow, 121552 Russian Federation	3807 15a, 3-d Cherepkovskaya street, Moscow, 121552 RUSSIAN FEDERATION Received drug	Site, Region: / Site, Central: / Site, Local: 24-Feb-15
Switzerland	Kantonale Ethikkommission Zürich (KEK) Kantonale Ethikkommission Zürich (KEK), Stampfenbachstrasse 121, Zürich, Zürich, 8090 Switzerland	2401 Rämistrasse 100, Klinik für Pneumologie, Zürich, ZH, 8091 SWITZERLAND Received drug	Site, Region: / Site, Central: / Site, Local: 18-Mar-15
Thailand	Research Ethics Chiang Mai University Research Ethics Chiang Mai University, Maharat Nakorn Chaingmai Hospital 110 Intrawaroros, Chiang Mai, 50200 Thailand	5701 Faculty of Medicine, Chiang Mai University, Department Of Internal Medicine, Chiang Mai, 50200 THAILAND Received drug	Site, Region: / Site, Central: / Site, Local: 26-May-14
Thailand	Institutional Review Board, Faculty of Medicine, Chulalongkorn University Institutional Review Board, Faculty of Medicine, Chulalongkorn University, 1873 Rama 4 Road, Pathumwan, Bangkok, 10330 Thailand	5704 1873 Rama 4 Road, Pathumwan, King Chulalongkorn memorial Hospital Thai Red Cross Society, Division Of Respiratory And Respiratory Critical Care Medicine, Department of Medicine, Bangkok, 10330 THAILAND Received drug	Site, Region: / Site, Central: / Site, Local: 3-Jul-14
Thailand	The Ethics Committee Faculty of Medicine Siriraj Hospital The Ethics Committee Faculty of Medicine Siriraj Hospital, 2 Prannok Road Bangkoknoi, Bangkok, 10700 Thailand	5705 2 Prannok Road, Bangkoknoi, Division Of Respiratory Disease And Tuberculosis, Bangkok, 10700 THAILAND Received drug	Site, Region: / Site, Central: / Site, Local: 23-Apr-14
Turkey	Istanbul University Istanbul Medical Faculty Clinical Research Ethical Committee Istanbul University Istanbul Medical Faculty Clinical Research Ethical Committee, FATIH CAPA 34093, Istanbul, 34093 Turkey	4202 Gogus Hastalıkları Ana Bilim Dalı, Capa_Istanbul, 34093 TURKEY Received drug	Site, Region: / Site, Central: 17-Mar-16 Site, Local: /
Ukraine	Ethics Committee of Communal Noncommercial Enterprise of Lviv Regional Council "Lviv Regional Clinical Hospital" Ethics Committee of Communal Noncommercial Enterprise of Lviv Regional Council "Lviv Regional Clinical Hospital", 7, Chernigivska	4100 7, Chernihivska St, Lviv, 79014 UKRAINE Received drug	Site, Region: / Site, Central: / Site, Local: 9-Jul-14

	Str., Lviv, 79010 Ukraine		
Ukraine	Local Ethics Committee of Public Institution "F.H. Yanovskyi Phthisiology and Pulmonology National Institute under the Ukrainian Academy of Medical Sciences" Local Ethics Committee of Public Institution "F.H. Yanovskyi Phthisiology and Pulmonology National Institute under the Ukrainian Academy of Medical Sciences", 10 Amosova str., Kyiv, 03680 Ukraine	4101 10, Amosova str, Kyiv, 03680 UKRAINE Received drug	Site, Region: / Site, Central: / Site, Local: 26-Sep-14
United Kingdom Of Great Britain And Northern Ireland	Imperial College London and Imperial College NHS Trust Imperial College London and Imperial College NHS Trust, Room 5L10A, 5th Floor, lab block, Charing Cross, London, W68RF United Kingdom Of Great Britain And Northern Ireland	2101 Du Cane Road, Shepherds Bush, Department of Cardiology, London, W12 0HS UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND Received drug	Site, Region: 22-Sep-14 Site, Central: 22-Sep-14 Site, Local: 16-Nov-15
United Kingdom Of Great Britain And Northern Ireland	LONDON - FULHAM LONDON - FULHAM, Barlow House 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ United Kingdom Of Great Britain And Northern Ireland	2101 Du Cane Road, Shepherds Bush, Department of Cardiology, London, W12 0HS UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND Received drug	Site, Region: 22-Sep-14 Site, Central: 22-Sep-14 Site, Local: 16-Nov-15
United Kingdom Of Great Britain And Northern Ireland	Health Research Authority Health Research Authority, 2 Redman Place, Stratford, London, E20 1JQ United Kingdom Of Great Britain And Northern Ireland	2101 Du Cane Road, Shepherds Bush, Department of Cardiology, London, W12 0HS UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND Received drug	Site, Region: 22-Sep-14 Site, Central: 22-Sep-14 Site, Local: 16-Nov-15
United Kingdom Of Great Britain And Northern Ireland	Papworth Hospital NHS Trust Papworth Hospital NHS Trust (Dept), Papworth Everard, Pulmonary Vascular Diseases Unit, Cambridge, CB23 3RE United Kingdom Of Great Britain And Northern Ireland	2102 Pulmonary Vascular Diseases Unit, Papworth Everard, Cambridge, CB23 3RE UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND Received drug	Site, Region: 22-Sep-14 Site, Central: 22-Sep-14 Site, Local: 3-Feb-15
United Kingdom Of Great Britain And Northern Ireland	Health Research Authority Health Research Authority, 2 Redman Place, Stratford, London, E20 1JQ United Kingdom Of Great Britain And Northern Ireland	2102 Pulmonary Vascular Diseases Unit, Papworth Everard, Cambridge, CB23 3RE UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND Received drug	Site, Region: 22-Sep-14 Site, Central: 22-Sep-14 Site, Local: 3-Feb-15

United Kingdom Of Great Britain And Northern Ireland	LONDON - FULHAM LONDON - FULHAM, Barlow House 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ United Kingdom Of Great Britain And Northern Ireland	2102 Pulmonary Vascular Diseases Unit, Papworth Everard, Cambridge, CB23 3RE UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND Received drug	Site, Region: 22-Sep-14 Site, Central: 22-Sep-14 Site, Local: 3-Feb-15
United Kingdom Of Great Britain And Northern Ireland	Sheffield Teaching Hospitals NHS Foundation Trust Sheffield Teaching Hospitals NHS Foundation Trust, Research Department, Clinical Research Office Sheffield, D Floor, Royal Hallamshire Hospital, Glossop Road, Sheffield, S10 2JF United Kingdom Of Great Britain And Northern Ireland	2104 Glossop Road, Pulmonary Vascular Medicine, Sheffield Teaching Hospitals, NHS Foundation Trust Royal Hallamshire Hospital Sheffield, S10 2RX UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND Received drug	Site, Region: 22-Sep-14 Site, Central: 22-Sep-14 Site, Local: 10-Dec-15
United Kingdom Of Great Britain And Northern Ireland	Health Research Authority Health Research Authority, 2 Redman Place, Stratford, London, E20 1JQ United Kingdom Of Great Britain And Northern Ireland	2104 Glossop Road, Pulmonary Vascular Medicine, Sheffield Teaching Hospitals, NHS Foundation Trust Royal Hallamshire Hospital Sheffield, S10 2RX UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND Received drug	Site, Region: 22-Sep-14 Site, Central: 22-Sep-14 Site, Local: 10-Dec-15
United Kingdom Of Great Britain And Northern Ireland	LONDON - FULHAM LONDON - FULHAM, Barlow House 3rd Floor, 4 Minshull Street, Manchester, M1 3DZ United Kingdom Of Great Britain And Northern Ireland	2104 Glossop Road, Pulmonary Vascular Medicine, Sheffield Teaching Hospitals, NHS Foundation Trust Royal Hallamshire Hospital Sheffield, S10 2RX UNITED KINGDOM OF GREAT BRITAIN AND NORTHERN IRELAND Received drug	Site, Region: 22-Sep-14 Site, Central: 22-Sep-14 Site, Local: 10-Dec-15

c). Scientific Committee members

China - Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Southern Medical University, Guangzhou: Prof. Zhi-Cheng Jing. **France** - Hôpital Bicêtre, Le Kremlin Bicêtre: Prof. G rald Simonneau. **Germany** - University of Giessen and Marburg Lung Center, Giessen: Prof. Hossein-Ardeschir Ghofrani; Kerckhoff-Klinik, Bad Nauheim: Prof. Eckhard Mayer. **Italy** - Foundation "I.R.C.C.S. Policlinico San Matteo", University of Pavia School of Medicine, Pavia: Prof. Andrea Maria D'Armini. **United Kingdom** - Hammersmith Hospital, London: Dr. Luke Howard; Royal Papworth

Hospital NHS Foundation Trust, Cambridge: Dr. David Jenkins. **USA** - University of California San Diego, La Jolla: Prof. Nick Kim.

d). Central Adjudication Committee members

France - Hôpital Bicêtre, Le Kremlin Bicêtre: Dr. Xavier Jaïs. **Germany** - Kerckhoff-Klinik, Bad Nauheim: Prof. Eckhard Mayer. **United Kingdom** - Royal Papworth Hospital NHS Foundation Trust, Cambridge: Dr. David Jenkins. **USA** - University of California San Diego, La Jolla: Prof. Peter Fedullo and Prof. Michael Madani.

e). Country-Specific Adjudication Committee members

China - Beijing Anzhen Hospital, Beijing: Prof. Hui-li Gan; FuWai Hospital, Beijing: Prof. Wei Fang; Guangdong Provincial People's Hospital, Guangdong Academy of Medical Sciences, Southern Medical University, Guangzhou: Prof. Zhi-Cheng Jing. **France** - Hôpital Bicêtre, Le Kremlin Bicêtre: Prof. Philippe Darteville, Prof. Elie Fadel, Prof. Gérald Simonneau and Prof. Olivier Sitbon. **Germany** - University of Giessen and Marburg Lung Center, Giessen: Prof. Hossein-Ardeschir Ghofrani, Prof. Gabriele Krombach and Dr. Henning Gall; Kerckhoff-Klinik, Bad Nauheim: Prof. Eckhard Mayer, Dr. Stefan Guth and Dr. Tamo Siemons. **Netherlands** - Vrije Universiteit Medical Centre, Amsterdam: Dr. Anco Boonstra, Dr. Petr Symersky and Prof. Anton Vonk Noordegraaf. **Poland** - Medicover Hospital, Warsaw: Prof. Andrzej Biederman; Instytut Kardiologii, Warsaw: Dr. Zbigniew Juraszynski. **Turkey** - Marmara University School of Medicine, Istanbul: Prof. Bedrettin Yıldızeli and Dr. Nuri Çagatay Çimsit. **United Kingdom** - Royal Papworth Hospital NHS Foundation Trust, Cambridge: Dr. Deepa Gopalan, Dr. David Jenkins, Dr. Joanna Pepke-Zaba, and Dr. Nicholas Screaton. **USA** - University of California San Diego, La Jolla: Prof. Peter Fedullo, Prof. Kim Kerr, Prof. Nick Kim, and Prof. Michael Madani.

f). Independent Liver Safety Data Review Board members

USA - University of Texas Southwestern Medical Center, Dallas: Prof. Willis Maddrey; University of North Carolina at Chapel Hill (UNC), Chapel Hill: Prof. Paul Watkins; Independent Pharmaceutical Consultant: Prof. James Freston.

The Independent Liver Safety Data Review Board was formed to provide ongoing assessment and advice regarding any serious hepatic events that required further evaluation. Two cases of hepatic adverse events of special interest were reviewed in MERIT-2

Supplementary Methods 2

Adverse events of special interest by Preferred term

Hepatic adverse events of special interest:

Increased alanine aminotransferase; increased alkaline phosphatase; increased aspartate aminotransferase; increased bilirubin; increased conjugated bilirubin; congestive hepatopathy; hepatic cirrhosis; hepatic cyst; hepatic encephalopathy; increased hepatic enzymes; hepatic pain; hepatitis; hyperbilirubinemia; hypertransaminasemia; increased liver function test.

Edema and Fluid Retention adverse events of special interest:

Peripheral edema; ascites; hydrothorax; edema; pericardial effusion; peripheral swelling; generalized edema; pleural effusion; joint swelling.

Anemia and Decrease of Hemoglobin adverse events of special interest:

Decreased hemoglobin; anemia; decreased hematocrit; hypochromic anemia; myelodysplastic syndrome; decreased red blood cell count.

Hypotension adverse events of special interest:

Decreased blood pressure; hypotension; orthostatic hypotension; syncope.

Supplementary Methods 3

China's Human Genetic Resources updated regulations

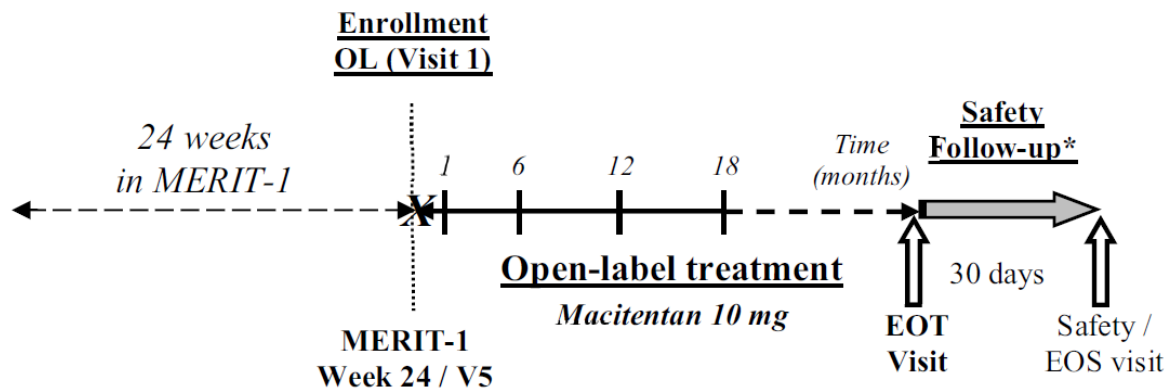
A potential compliance issue with China's Human Genetic Resources (HGR) regulations was identified in early 2020. The Office of Human Genetic Resources (OHGRA) issues approvals for foreign companies to utilize and transfer human biospecimens and related data collected through clinical trials conducted in China. The rules on data transfer include restrictions on exportation of samples and data. Over the course of MERIT-2, the HGR rules and OHGRA policies and practices changed and under these new stipulations, a requirement from the Human Genetics Resources Administration of China (HGRAC) applicable to this study was not fulfilled. Assessments by the sponsor determined that the probability of obtaining retrospective OHGRA approval to export clinical data—in particular, but not limited to, data related to blood samples—outside of China was low. To prevent violation of the HGR Regulations, the decision was made to halt the collection and transfer of data for the Chinese patients ongoing in the study.

The following restrictions were applied:

1. From 09 July 2020, no further data were collected for the study (i.e., no further entry of data into the electronic case report forms or to the sponsor's clinical database).
2. From 13 April 2020, safety assessments were performed at local laboratories only (i.e., not performed by the central laboratory) and the results were not shared with sponsor.
 - SAEs/pregnancies continued to be reported to the sponsor's global safety database.
3. To maintain alignment with other Health Authority safety data analyses, the sponsor applied an analysis data cut-off date of 17 October 2019 for the participants at sites in China.
 - Information on significant safety events (i.e., deaths, SAEs, pregnancies) occurring after 17 October 2019 was therefore solely obtained from the sponsor's global safety database.

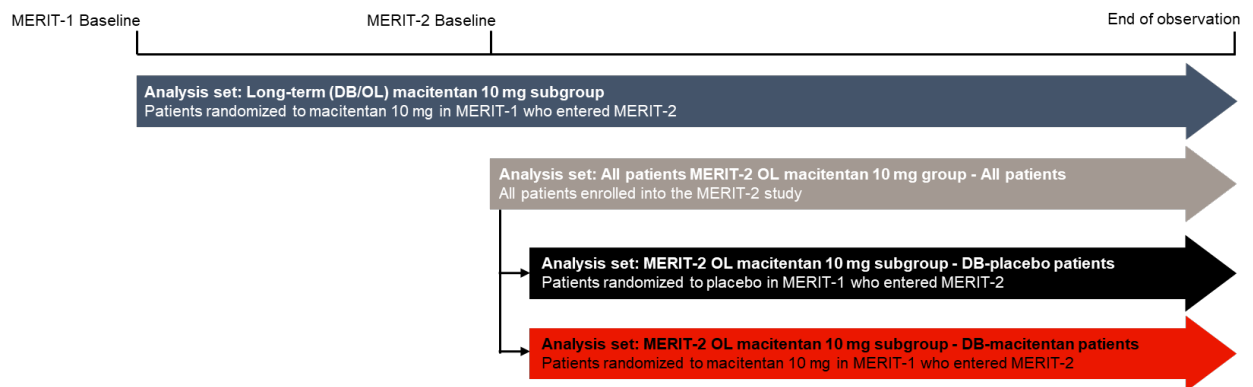
Neither the safety of the trial participants nor the scientific value of the trial was impacted. The trial was conducted in accordance with principles equivalent to the provisions of Directive 2001/20/EC and there was no breach of participant privacy or confidentiality

Figure S1. Study design



*For participants who entered a continued access program (post-trial access program or other OL study), enrollment into the continued access program occurred on the day of the last visit of the MERIT-2 study (EOS, which corresponded to EOT visit in this case). EOS: end of study; EOT: end of treatment; OL: open-label; V: visit

Figure S2. Analysis sets



DB: double blind; OL: open-label.

Table S1. Exposure, adverse events and adverse events of special interest for the sensitivity analyses

	Observation commencing from MERIT-2 enrollment			Observation commencing from MERIT-1 enrollment
	MERIT-2 OL macitentan 10 mg group			Long-term (DB/OL) macitentan 10 mg subgroup N=30
	All patients N=57	DB-placebo patients N=27	DB-macitentan patients N=30	
Exposure^a, months, median (Q1, Q3)	56.6 (18.8, 67.4)	63.7 (18.3, 69.5)	46.7 (18.8, 66.3)	52.4 (24.6, 71.8)
Patient with ≥1 adverse events, n (%)				
Adverse event	55 (96.5)	27 (100.0)	28 (93.3)	30 (100.0)
Serious adverse event	35 (61.4)	17 (63.0)	18 (60.0)	19 (63.3)
Adverse event leading to treatment discontinuation	9 (15.8)	4 (14.8)	5 (16.7)	5 (16.7)
Most frequent adverse events^b, n (%)				
Worsening of pulmonary hypertension	12 (21.1)	5 (18.5)	7 (23.3)	7 (23.3)
Peripheral edema	11 (19.3)	5 (18.5)	6 (20.0)	13 (43.3)
Anemia	10 (17.5)	8 (29.6)	2 (6.7)	3 (10.0)
Decreased hemoglobin	9 (15.8)	6 (22.2)	3 (10.0)	4 (13.3)
Bronchitis	9 (15.8)	5 (18.5)	4 (13.3)	4 (13.3)
Dizziness	8 (14.0)	3 (11.1)	5 (16.7)	6 (20.0)
Dyspnea	8 (14.0)	3 (11.1)	5 (16.7)	6 (20.0)
Cardiac failure	7 (12.3)	2 (7.4)	5 (16.7)	6 (20.0)
Cough	7 (12.3)	4 (14.8)	3 (10.0)	5 (16.7)
Diarrhea	7 (12.3)	5 (18.5)	2 (6.7)	3 (10.0)
Headache	7 (12.3)	5 (18.5)	2 (6.7)	3 (10.0)
Upper respiratory tract infection	7 (12.3)	2 (7.4)	5 (16.7)	6 (20.0)
Cataract	7 (12.3)	4 (14.8)	3 (10.0)	3 (10.0)
Urinary tract infection	6 (10.5)	2 (7.4)	4 (13.3)	6 (20.0)
Pain in extremity	6 (10.5)	2 (7.4)	4 (13.3)	5 (16.7)
Arterial angioplasty	6 (10.5)	3 (11.1)	3 (10.0)	3 (10.0)
COVID-19	6 (10.5)	3 (11.1)	3 (10.0)	3 (10.0)
Nasopharyngitis	6 (10.5)	4 (14.8)	2 (6.7)	2 (6.7)
Syncope	6 (10.5)	1 (3.7)	5 (16.7)	5 (16.7)
Right ventricular failure	5 (8.8)	1 (3.7)	4 (13.3)	5 (16.7)
Weight decreased	5 (8.8)	5 (18.5)	0	1 (3.3)

Back pain	5 (8.8)	4 (14.8)	1 (3.3)	1 (3.3)
Osteoarthritis	5 (8.8)	4 (14.8)	1 (3.3)	1 (3.3)
Arthralgia	4 (7.0)	3 (11.1)	1 (3.3)	2 (6.7)
Hyperuricemia	4 (7.0)	1 (3.7)	3 (10.0)	3 (10.0)
Pyrexia	4 (7.0)	1 (3.7)	3 (10.0)	3 (10.0)
Respiratory tract infection viral	4 (7.0)	1 (3.7)	3 (10.0)	3 (10.0)
Sleep apnea syndrome	4 (7.0)	0	4 (13.3)	4 (13.3)
Ascites	3 (5.3)	0	3 (10.0)	3 (10.0)
Abdominal discomfort	3 (5.3)	1 (3.7)	2 (6.7)	3 (10.0)
Hemorrhoids	3 (5.3)	1 (3.7)	2 (6.7)	3 (10.0)
Cystitis	3 (5.3)	3 (11.1)	0	0
Dyslipidemia	3 (5.3)	0	3 (10.0)	3 (10.0)
Hypercholesterolemia	3 (5.3)	3 (11.1)	0	0
Iron deficiency	3 (5.3)	3 (11.1)	0	0
Nausea	3 (5.3)	3 (11.1)	0	0
Pulmonary embolism	3 (5.3)	1 (3.7)	2 (6.7)	2 (6.7)
Rash	3 (5.3)	0	3 (10.0)	3 (10.0)
Hydrothorax	2 (3.5)	0	2 (6.7)	3 (10.0)
Adverse events of special interest				
Edema and fluid retention, n (%)	20 (35.1)	7 (25.9)	13 (43.3)	18 (60.0)
Incidence rate – per 100 person-year (95% CI)	11.4 (7.3, 17.7)	7.8 (3.7, 16.5)	15.1 (8.7, 25.9)	26.8 (16.8, 42.6)
Anemia / hemoglobin decrease, n (%)	17 (29.8)	13 (48.1)	4 (13.3)	5 (16.7)
Incidence rate – per 100 person-year (95% CI)	9.9 (6.1, 15.9)	17.1 (9.9, 29.4)	4.2 (1.6, 11.1)	4.6 (1.9, 11.1)
Hepatic AESI, n (%)	10 (17.5)	4 (14.8)	6 (20.0)	6 (20.0)
Incidence rate – per 100 person-year (95% CI)	4.9 (2.6, 9.1)	3.8 (1.4, 10.2)	5.9 (2.7, 13.2)	5.4 (2.4, 12.0)
Hypotension, n (%)	10 (17.5)	3 (11.1)	7 (23.3)	7 (23.3)
Incidence rate – per 100 person-year (95% CI)	5.0 (2.7, 9.3)	3.0 (1.0, 9.2)	7.1 (3.4, 14.9)	6.2 (3.0, 13.1)
Deaths, n (%)	14 (24.6)	6 (22.2)	8 (26.7)	8 (26.7)

Sensitivity analyses presenting data excluding patients from Chinese sites ongoing at the cut-off date. Treatment emergent periods were defined as follows: MERIT-2 OL macitentan 10 mg group: Treatment start date in MERIT-2 OL, up to 30 days after end of treatment in MERIT-2 OL; Long-term (DB/OL) macitentan 10 mg subgroup: Start of macitentan in MERIT-1 DB, up to 30 days after end of treatment in MERIT-2 OL. ^aFor OL datasets, exposure refers to OL exposure to macitentan 10 mg; for DB/OL dataset, exposure refers to cumulative DB/OL exposure to macitentan 10 mg. ^bAdverse events ≥10% in any group, by Preferred Term. AESI: Adverse event of special interest; CI: confidence interval; DB: double-blind; OL: open-label; Q1, Q3: interquartile range.

Table S2. Serious adverse events for main analyses (a) and sensitivity analyses (b)

a) Main analyses

	Observation commencing from MERIT-2 enrollment			Observation commencing from MERIT-1 enrollment
	MERIT-2 OL macitentan 10 mg group			Long-term (DB/OL) macitentan 10 mg subgroup N=40
	All patients N=76	DB-placebo patients N=36	DB-macitentan patients N=40	
Patient with ≥ 1 serious adverse events, n (%)	44 (57.9)	19 (52.8)	25 (62.5)	26 (65.0)
Most frequent serious adverse events^a, n (%)				
Arterial angioplasty ^b	7 (9.2)	3 (8.3)	4 (10.0)	4 (10.0)
Worsening of pulmonary hypertension	6 (7.9)	2 (5.6)	4 (10.0)	4 (10.0)
Right ventricular failure	5 (6.6)	1 (2.8)	4 (10.0)	4 (10.0)
Cardiac failure	4 (5.3)	1 (2.8)	3 (7.5)	3 (7.5)
Pneumonia	4 (5.3)	2 (5.6)	2 (5.0)	2 (5.0)
Acute cardiac failure	3 (3.9)	2 (5.6)	1 (2.5)	1 (2.5)
Angioplasty ^b	3 (3.9)	1 (2.8)	2 (5.0)	2 (5.0)
Death	3 (3.9)	1 (2.8)	2 (5.0)	2 (5.0)
Lumbar vertebral fracture	3 (3.9)	0	3 (7.5)	3 (7.5)
Pulmonary embolism	3 (3.9)	1 (2.8)	2 (5.0)	2 (5.0)
Hemoptysis	2 (2.6)	2 (5.6)	0	0
Pyrexia	2 (2.6)	0	2 (5.0)	2 (5.0)
Reperfusion injury	2 (2.6)	0	2 (5.0)	2 (5.0)

b) Sensitivity analyses (excluding patients from Chinese sites [n=19] ongoing at the cut-off date)

	Observation commencing from MERIT-2 enrollment			Observation commencing from MERIT-1 enrollment
	MERIT-2 OL macitentan 10 mg group			Long-term (DB/OL) macitentan 10 mg subgroup N=30
	All patients N=57	DB-placebo patients N=27	DB-macitentan patients N=30	
Patient with ≥1 serious adverse events, n (%)	35 (61.4)	17 (63.0)	18 (60.0)	19 (63.3)
Most frequent serious adverse events^a, n (%)				
Arterial angioplasty ^b	6 (10.5)	3 (11.1)	3 (10.0)	3 (10.0)
Right ventricular failure	5 (8.8)	1 (3.7)	4 (13.3)	4 (13.3)
Cardiac failure	4 (7.0)	1 (3.7)	3 (10.0)	3 (10.0)
Worsening of pulmonary hypertension	4 (7.0)	1 (3.7)	3 (10.0)	3 (10.0)
Acute cardiac failure	3 (5.3)	2 (7.4)	1 (3.3)	1 (3.3)
Death	3 (5.3)	1 (3.7)	2 (6.7)	2 (6.7)
Lumbar vertebral fracture	2 (3.5)	0	2 (6.7)	2 (6.7)
Reperfusion injury	2 (3.5)	0	2 (6.7)	2 (6.7)

Treatment emergent periods were defined as follows: MERIT-2 OL macitentan 10 mg group: Treatment start date in MERIT-2 OL, up to 30 days after end of treatment in MERIT-2 OL; Long-term (DB/OL) macitentan 10 mg subgroup: Start of macitentan in MERIT-1 DB, up to 30 days after end of treatment in MERIT-2 OL. ^aSerious adverse events ≥5% in any group, by Preferred Term. ^bThese terms refer to balloon pulmonary angioplasty and were reported as serious adverse events due to the requirement for hospitalization. DB: double-blind; OL: open-label.

Table S3. Adverse events leading to discontinuation for main analyses (a) and sensitivity analyses (b)

a) Main analyses

	Observation commencing from MERIT-2 enrollment			Observation commencing from MERIT-1 enrollment
	MERIT-2 OL macitentan 10 mg group			Long-term (DB/OL) macitentan 10 mg subgroup N=40
	All patients N=76	DB-placebo patients N=36	DB-macitentan patients N=40	
Patients with ≥1 adverse event leading to treatment discontinuation, n (%)	9 (11.8)	4 (11.1)	5 (12.5)	5 (12.5)
Anemia	1 (1.3)	0	1 (2.5)	1 (2.5)
Asthenia	1 (1.3)	0	1 (2.5)	1 (2.5)
Breast cancer	1 (1.3)	0	1 (2.5)	1 (2.5)
Breast cancer metastatic	1 (1.3)	0	1 (2.5)	1 (2.5)
Fall	1 (1.3)	0	1 (2.5)	1 (2.5)
Decreased hemoglobin	1 (1.3)	1 (2.8)	0	0
Intercranial hemorrhage	1 (1.3)	0	1 (2.5)	1 (2.5)
Head injury	1 (1.3)	0	1 (2.5)	1 (2.5)
Increased Liver function test	1 (1.3)	1 (2.8)	0	0
Pneumonia	1 (1.3)	1 (2.8)	0	0
Pulmonary embolism	1 (1.3)	0	1 (2.5)	1 (2.5)
Pulmonary endarterectomy	1 (1.3)	1 (2.8)	0	0
Pulmonary tuberculosis	1 (1.3)	0	1 (2.5)	1 (2.5)
Right ventricular failure	1 (1.3)	0	1 (2.5)	1 (2.5)
Somnolence	1 (1.3)	0	1 (2.5)	1 (2.5)

b) **Sensitivity analyses** (excluding patients from Chinese sites [n=19] ongoing at the cut-off date)

	Observation commencing from MERIT-2 enrollment			Observation commencing from MERIT-1 enrollment
	MERIT-2 OL macitentan 10 mg group			Long-term (DB/OL) macitentan 10 mg subgroup
	All patients N=57	DB-placebo patients N=27	DB-macitentan patients N=30	N=30
Patients with ≥1 adverse event leading to treatment discontinuation, n (%)	9 (15.8)	4 (14.8)	5 (16.7)	5 (16.7)
Anemia	1 (1.8)	0	1 (3.3)	1 (3.3)
Asthenia	1 (1.8)	0	1 (3.3)	1 (3.3)
Breast cancer	1 (1.8)	0	1 (3.3)	1 (3.3)
Breast cancer metastatic	1 (1.8)	0	1 (3.3)	1 (3.3)
Fall	1 (1.8)	0	1 (3.3)	1 (3.3)
Decreased hemoglobin	1 (1.8)	1 (3.7)	0	0
Intercranial hemorrhage	1 (1.8)	0	1 (3.3)	1 (3.3)
Head injury	1 (1.8)	0	1 (3.3)	1 (3.3)
Increased liver function test	1 (1.8)	1 (3.7)	0	0
Pneumonia	1 (1.8)	1 (3.7)	0	0
Pulmonary embolism	1 (1.8)	0	1 (3.3)	1 (3.3)
Pulmonary endarterectomy	1 (1.8)	1 (3.7)	0	0
Pulmonary tuberculosis	1 (1.8)	0	1 (3.3)	1 (3.3)
Right ventricular failure	1 (1.8)	0	1 (3.3)	1 (3.3)
Somnolence	1 (1.8)	0	1 (3.3)	1 (3.3)

Treatment emergent periods were defined as follows: MERIT-2 OL macitentan 10 mg group: Treatment start date in MERIT-2 OL, up to 30 days after end of treatment in MERIT-2 OL; Long-term (DB/OL) macitentan 10 mg subgroup: Start of macitentan in MERIT-1 DB, up to 30 days after end of treatment in MERIT-2 OL. DB: double-blind; OL: open-label.

Table S4. Causes of death for main analyses (a) and sensitivity analyses (b)

a) Main analyses

	Observation commencing from MERIT-2 enrollment			Observation commencing from MERIT-1 enrollment
	MERIT-2 OL macitentan 10 mg group			Long-term (DB/OL) macitentan 10 mg subgroup N=40
	All patients N=76	DB-placebo patients N=36	DB-macitentan patients N=40	
Deaths, n (%)	14 (18.4)	6 (16.7)	8 (20.0)	8 (20.0)
Causes (Preferred Term), n (%)				
Aggravated cardiac failure	2 (2.6)	0	2 (5.0)	2 (5.0)
Acute heart failure	2 (2.6)	1 (2.8)	1 (2.5)	1 (2.5)
Heart failure	1 (1.3)	0	1 (2.5)	1 (2.5)
Right ventricular failure	1 (1.3)	0	1 (2.5)	1 (2.5)
Acute cardiac insufficiency	1 (1.3)	1 (2.8)	0	0
Multiorgan failure	1 (1.3)	1 (2.8)	0	0
Respiratory tract infection	1 (1.3)	0	1 (2.5)	1 (2.5)
Septic shock	1 (1.3)	1 (2.8)	0	0
CTEPH	1 (1.3)	1 (2.8)	0	0
Unknown	3 (3.9)	1 (2.8)	2 (5.0)	2 (5.0)

b) Sensitivity analyses (excluding patients from Chinese sites [n=19] ongoing at the cut-off date)

	Observation commencing from MERIT-2 enrollment			Observation commencing from MERIT-1 enrollment
	MERIT-2 OL macitentan 10 mg group			Long-term (DB/OL) macitentan 10 mg subgroup N=30
	All patients N=57	DB-placebo patients N=27	DB-macitentan patients N=30	
Deaths, n (%)	14 (24.6)	6 (22.2)	8 (26.7)	8 (26.7)
Causes (Preferred Term), n (%)				
Aggravated cardiac failure	2 (3.5)	0	2 (6.7)	2 (6.7)
Acute heart failure	2 (3.5)	1 (3.7)	1 (3.3)	1 (3.3)
Heart failure	1 (1.8)	0	1 (3.3)	1 (3.3)
Right ventricular failure	1 (1.8)	0	1 (3.3)	1 (3.3)
Acute cardiac insufficiency	1 (1.8)	1 (3.7)	0	0
Multiorgan failure	1 (1.8)	1 (3.7)	0	0
Respiratory tract infection	1 (1.8)	0	1 (3.3)	1 (3.3)
Septic shock	1 (1.8)	1 (3.7)	0	0
CTEPH	1 (1.8)	1 (3.7)	0	0
Unknown	3 (5.3)	1 (3.7)	2 (6.7)	2 (6.7)

CTEPH: chronic thromboembolic pulmonary hypertension; DB: double-blind; OL: open-label.